REMARKS/ARGUMENTS

Applicants respectfully note again that the Attorney Docket Number for this application has been changed from 20164000US5 to ARG010RC; correction of the Attorney Docket Number for this application is respectfully requested.

Claims 99, 101, 104-113, 116, 120, and 142-144 are pending in the application. Applicants acknowledge with appreciation the Examiner's reconsideration and withdrawal of one of the previously asserted grounds for denying priority (Office Action, page 2, #3). Independent claims 101 and 120 (and thus also the other pending claims, which are dependent on or incorporate the limitations of these claims) have been amended to more closely reflect the language in the application verbatim. Dependent claim 99 was also amended to maintain consistent terminology throughout the claims.

No new matter has been added by way of amendment. Reconsideration and reexamination of the claims are respectfully requested.

The Claim of Priority Should Be Accepted

Applicants gratefully acknowledge that the Office Action (dated November 18, 2008, page 2, #3) states that one of the grounds for denying priority has been withdrawn and that another has been rendered moot. Unfortunately, the Office Action apparently still concludes that the benefit of priority to earlier applications should be denied because "neither the '612 nor the '357 applications disclose the cells being cultured with an antigen as is recited in the last step of Claims 101 and 120" (Office Action at page 2, #3, first paragraph, referring to the priority Applications Nos. 07/861,612 and 07/981,357). Applicants respectfully disagree with the analysis and conclusion set forth in the Office Action, but nevertheless, in an effort to advance prosecution, have amended the language of independent claims 101 and 120 to more closely reflect the language in the application verbatim. Applicants respectfully submit that the claims as amended have essentially the same meaning and scope as the claims prior to amendment (see, *e.g.*, the '612 application at page 6, lines 8-14), but are hopeful that the amendments will overcome the objection to the claims. (In order to

clearly address the concerns in the Office Action, the discussion in this response focuses on the first-filed '612 priority application, but the other applications in the priority chain also provide support for the claims as set forth herein for the '612 application.)

Claims 101 and 120 have been amended to specify that the dendritic cells are contacted *in vitro* with antigen in the presence of GM-CSF for a sufficient time to allow the antigen to bind to the dendritic cells, wherein the dendritic cells process the antigen to produce a modified antigen which is expressed by the dendritic cells. Support for this amendment can be found in the present application (*e.g.*, on page 34, line 33 through page 35, line 3) as well as in the '612 priority application on page 22, lines 10-20, which state:

> The antigen-activated dendritic cells of the invention are produced by exposing antigen, *in vitro*, to the dendritic cells prepared according to the method of the invention. Dendritic cells are plated in culture dishes and exposed to antigen in a sufficient amount and **for a sufficient period of time to allow the antigen to bind to the dendritic cells.**"

Further support for this amendment can be found in the original claims of the '612 priority application, particularly claims 36 and 17, which were as follows:

> 36. A composition comprising antigen-activated dendritic cells **wherein dendritic cells prepared according to claim 17 are pulsed with an antigen** and **wherein the dendritic cells process the antigen to produce a modified antigen which is expressed by the dendritic cells.**
>
> 17. A method of producing a population of mature dendritic cells from proliferating cell cultures comprising:
>
> a) providing a tissue source comprising dendritic cell precursors;
>
> b) treating the tissue source to obtain a population of cells suitable for culture *in vitro*;
>
> c) culturing the tissue source on a substrate in a culture medium comprising GM-CSF to obtain nonadherent cells and cell clusters;
>
> d) subculturing the nonadherent cells and cell clusters to produce cell aggregates comprising proliferating dendritic cell precursors;

> e) serially subculturing the cell aggregates one or more time to enrich the proportion of dendritic cell precursors; and
> f) continuing to culture the dendritic cell precursors for a period of time sufficient to allow them to mature into mature dendritic cells.

A comparison of these original claims of the '612 application to amended claim 101 shows that the limitations are essentially the same; accordingly, Applicants respectfully submit that claim 101 is fully supported by the '612 priority application.

Support for independent claim 101 can also be found, for example, in the '612 application on page 8, lines 15-19 (stating that "[a]nother embodiment of the invention [is] **antigen-activated dendritic cells prepared according to the method of the invention** [in] which antigen-activated dendritic cells have been exposed to antigen and express modified antigens for presentation to and activation of T cells") and on page 10, lines 2-5 (stating that **"[a]nother object of this invention is to provide novel immunogens comprising the dendritic cells of this invention which have been exposed to antigen and express modified antigen on their surface"**).

Similarly, amended claim 120 specifies "[a]n *in vitro* composition comprising mature dendritic cells derived from an *in vitro* culture of a population of enriched and expanded proliferating precursor cells, wherein said dendritic cells are contacted *in vitro* with antigen in the presence of GM-CSF for a sufficient time to allow the antigen to bind to the dendritic cells, wherein the dendritic cells process the antigen to produce a modified antigen which is expressed by the dendritic cells." Support for claim 120 can be found, for example, in the '612 application on page 8, lines 15-19, which state: "Another embodiment of the invention [is] antigen-activated dendritic cells prepared according to the method of the invention [in] which antigen-activated **dendritic cells have been exposed to antigen and express modified antigens for presentation to and activation of T cells**." The '612 application explains on page 22, lines 10-20, that "[t]he **antigen-activated dendritic cells of the invention are produced by exposing antigen, *in vitro*, to the dendritic cells prepared according to the method of the invention**. Dendritic cells are plated in culture dishes and exposed to antigen in a

sufficient amount and for a sufficient period of time to allow the antigen to bind to the dendritic cells."

Claim 99 has been amended similarly to claims 101 and 120 to maintain consistency in the language of the claims and now specifies: "[t]he pharmaceutical composition according to claim 116, wherein the dendritic cells express an amount of the modified antigen to provide between about 1 to 100 micrograms of the modified antigen in said pharmaceutical composition." Support for this amendment can be found in the '612 application, for example, on page 24, lines 7-13, which state that "[t]he vaccines or pharmaceutical compositions comprising the modified antigens or the antigen-activated dendritic cells of the invention would be administered in therapeutically effective amounts sufficient to elicit an immune response. Preferably, between about 1 to 100 micrograms of modified antigen, or its equivalent when bound to dendritic cells, should be administered per dose."

The same language cited above from the '612 application is also found in every application in the priority chain, including the instant application (No. 09/073,596). The discussion of support for the other pending claims was included in detail in the previous reply and was not commented on negatively in the outstanding Office Action, so it is not reproduced here. In view of the support in the applications for the amended claims, Applicants respectfully submit that the claims are fully supported by the specification(s), including the first-filed priority application, and that the priority claim should be given full weight.

The Rejections of Claims under 35 U.S.C. § 102 Should Be Withdrawn

The Office Action (page 3, #5) has maintained the rejection of claims 99, 101, 104-113, 116, 120, and 142-144 under 35 U.S.C. § 102(a) over Pancholi *et al.* (1992) *Immunology* 76: 217-224. The Office Action states (page 3, paragraphs 7 and 8) that the claims are not entitled to the priority date of App. No. 07,861,612 ("the '612 application") and that therefore the Pancholi reference is available as prior art, even

though it was published after the priority date of the '612 application. Applicants respectfully disagree with this conclusion and traverse this rejection.

As discussed above, independent claims 101 and 120 and dependent claim 99 (as well as the other pending claims, which all depend from or incorporate the limitations of claims 101 or 120) have been amended to more closely reflect the language of the '612 priority application. In view of the support in the '612 application for the pending claims, as discussed in detail above, Applicants respectfully submit that the claims are entitled to the '612 priority date (*i.e.*, April 1, 1992) and that Pancholi therefore is not available as prior art against the claims. Accordingly, Applicants request that this rejection of claims be reconsidered and withdrawn.

The Office Action (page 3, #9) has also rejected claims 101, 104-113, 116, and 120 under 35 U.S.C. §102(b) over Steinman *et al.* (1974) as evidenced by O'Doherty (1994). The Office Action states (page 4, first full paragraph) that "Steinman et al. teaches an in vitro composition comprising a mature DC...." and concludes that "[t]he reference clearly anticipates the claimed invention." Applicants respectfully disagree with this conclusion and traverse the rejection.

Specifically, the Steinman reference discusses properties of freshly isolated cells from mouse spleen ("fresh spleen cells"). Fresh spleen cells differ in at least several critical ways from the *in vitro* compositions of the present invention, as evidenced, for example, by the Inaba reference (Inaba *et al.* (1990) *J. Exp. Med.* 172: 631-640, discussed previously, for example, in the Office Action of 2 July 2002). First, as taught by the Inaba reference, fresh spleen cells can only take up antigens for a short time, and lose this ability after only a day in culture. In contrast, the cells of the present invention can take up antigen after being cultured for many days (see, *e.g.*, Figure 13, showing uptake and expression of antigen after cells had been cultured for 6 days in GM-CSF). Further, because fresh spleen cells lose their ability to take up antigen after only a day in culture, fresh spleen cells cannot give rise to enriched and expanded cell populations which take up antigen, as required by the present claims. In contrast, the

present invention provides enriched and expanded cell populations in clinically useful quantities (see, *e.g.*, '612 application at page 7, first paragraph and the present specification at page 40, lines 25-28).

Applicants respectfully note that when product-by-process claims are examined, "[t]he structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where the product can only be defined by the process steps by which the product is made, or where the manufacturing process steps would be expected to impart distinctive structural characteristics to the final product" (MPEP § 2113). Here, the claims are drawn to an *in vitro* composition of cells derived from an *in vitro* culture of an enriched and expanded population of proliferating precursors by a method comprising culture in GM-CSF, which surprisingly was found to promote that proliferation (see, *e.g.*, '612 application on page 16, lines 2-6, stating that "GM-CSF has surprisingly been found to promote the proliferation *in vitro* of precursor dendritic cells"; and on page 16, lines 23-24, stating that "[i]n the absence of GM-CSF, no colonies develop"). Thus, the '612 application (as well as the present specification) teaches that **culture of the cells *in vitro* in GM-CSF provides the enriched and expanded population of proliferating dendritic cell precursors required by the present claims, and these cells differ from previously reported cells**, for example, in their ability to take up antigen even after extended periods of culture.

Because the fresh spleen cells taught by the Steinman reference are indistinguishable from the fresh spleen cells taught by the previously cited Inaba reference, Applicants respectfully urge that the rejection over the Steinman reference be withdrawn for the same reason that the rejection over the Inaba reference was previously withdrawn (see, *e.g.*, the Office Action of 13 August 2004, page 2, #2); specifically, that the cells taught by the reference are not the same as the cells of the instant invention because they were not cultured in GM-CSF. As discussed above, culture in GM-CSF is essential to the development of *in vitro* cultures of proliferating precursor cells of the present claims. None of the cited references has taught this critical feature of the invention. Accordingly, the claimed invention cannot be

anticipated by or rendered obvious by any of these references and Applicants respectfully request that these rejections of the claims be withdrawn.

CONCLUSION

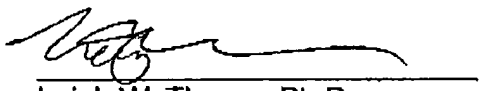
In view of the foregoing remarks, Applicants respectfully submit that the rejections of claims have been overcome and that the claims are in condition for allowance. However, if the Examiner believes that any further discussion of this communication would be helpful, he is encouraged to contact the undersigned by telephone.

Applicants hereby request a One Month Extension of Time for submitting this Amendment. The Commissioner is authorized to charge Deposit Account No. 50-3187 in the amount of $130.00.

Applicants enclose a Request for Continued Examination (RCE) Transmittal. The Commissioner is authorized to charge Deposit Account No. 50-3187 in the amount of $810.00.

No additional fees or extensions of time are believed to be due in connection with this communication except for those indicated in documents accompanying this paper. However, if any additional extensions of time are necessary for the consideration of this paper, such extensions are petitioned under 37 CFR § 1.136(a). Please apply any charges that may be due for extensions of time or for net addition of claims to our Deposit Account No. 50-3187.

Respectfully submitted,



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